understanding of these assembly pathways is of significant importance for both development of amyloids as functional nanomaterials, as well the biological understanding of amyloidosis. Using fluctuation microscopy and imaging, we have previously demonstrated that the nucleation of Amyloid-ß(16-22) peptide, the nucleating core of Amyloid-ß, initiates within dense unstructured peptide aggregates, and elongation proceeds via monomer addition to the active ends of growing nanostructures (Liang *et al*, J. Am. Chem. Soc. 2010, 132, 6306-6308). This previous work utilized a Rhodamine-labeled amyloid peptide (Rh1722), which co-assembles with Amyloid- ß(16-22) without affecting the morphology of the nanostructures. In order to further investigate the mechanisms of assembly at a molecular level, we are using Fluorescence Lifetime Imaging Microscopy (FLIM) to probe the lifetime of Rh1722. Rh1722 is highly sensitive to the local environment, and thus its fluorescence lifetime serves as a sensitive indicator of local amyloid environment and inferred structure. Our initial studies have revealed distinct fluorescence lifetime values within amyloid aggregates compared to nanotubes, suggesting that this technique will allow us to follow details at the molecular level in the nucleation, growth, and maturation processes. We also have evidence for the existence of nucleating cores within the unstructured peptide aggregates. These observations and future studies will further inform our understanding of amyloid nucleation and growth.

This work is supported by NSF grants MCB-0817966 and DMR-0907435.

1102-Pos Board B12

Alzheimer Aβ Aggregation on Controlled Self-Assembled Monolayers

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Self-assembly of unstructured protein/peptide monomers into highly ordered, misfolded protein aggregates is associated with many neurodegenerative diseases, including Alzheimer's, Parkinson's, and type II diabetes. Despite significant progress on the characterization of atomic details of amyloid-β (Aβ) fibrils, much less is known about the structure and kinetics of Aβ intermediate species during the early stage of aggregation, in particular about Aβ interactions with cell membranes, which is more biological relevance for understanding the mechanism of neurotoxicity. But, due to complex nature of cell membranes and notorious environmental sensitivity of Aβ aggregation, the study of Aβ-membrane interactions is particularly challenging, often leading to inconsistent data and controversial explanations of Aβ toxicity.

In this work, we use alternative, molecular-designed self-assembled monolayers (SAMs) as a surface template to systematically study Aβ structure and aggregation behaviors on the SAMs using molecular dynamics simulation and experimental approaches (CD, AFM, SPR, and DLS). Four types of the SAMs terminated with hydrophobic -CH_3, hydrophilic -OH, negatively charged -COOH, and positively charged -NH_2 groups are used to mimic certain surface chemistry of cell membranes and decouple these surface properties separately to examine their impacts on modulating Aβ structures and kinetics at early aggregation process. Our results show that: (1) all SAMs significantly accelerate Aβ fibril formation as compared to in bulk solution; (2) hydrophobic CH_3-SAM surface induces more Aβ adsorption with the strongest binding affinity, as compared to other SAMs, indicating that hydrophobic interactions are major driving forces for Aβ aggregation; (3) Aβ adsorption amount on the SAMs is strongly depended on Aβ aggregated state in solution, i.e. Aβ adsorption is reduced when Aβ peptides form a hydrophobic core by C-terminal residues protected by hydrophilic N-terminals in solution. This work provides parallel and valuable insights into Aβ aggregation on the cell membranes.

1103-Pos Board B13

Solid State NMR of Fibrillar Beta Amyloid Isoforms

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The 40-43 residue-long beta amyloid peptides aggregate in the extracellular neuronal space to form amyloid plaques, which contain numerous beta amyloid fibrils. Biological interest in amyloid fibrils arises from their occurrence in amyloid diseases, such as Alzheimer's disease (AD). The truncated pyroglutamate beta amyloid (p3-42) and beta amyloid (4-42) peptides are two of the most dominant isoforms found in excised amyloid material from AD brains. We investigate the self-seeding and cross-seeding behavior of the different amyloid beta isoforms, and utilize magic angle spinning NMR techniques to study the molecular structure of the fibrils formed by the amyloid beta (p3-42) and (4-42) peptides. The structures of these fibrils are compared to the available structures of the wild type and mutant beta amyloid (1-40) and (1-42) fibrils.

1104-Pos Board B14

Ultraviolet Resonance Raman Studies of a Disordered Peptide

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The amyloid-β (Aβ) peptide, a major component of the insoluble plaques associated with Alzheimer's disease, is intrinsically disordered under physiological conditions. Many polyphenolic compounds disrupt aggregation of Aβ *in vitro*. Interestingly, these compounds have been shown to interact with other disordered proteins through hydrophobic and aromatic interactions, as well as, hydrogen bonding with the peptide backbone. Deep-ultraviolet resonance Raman (UVRR) studies of Aβ (1-42) indicate that the environment of at least one of the phenylalanine residues is altered upon introduction of the polyphenolic flavonoid myricetin.

1105-Pos Board B15

Structural Consequences of Epitaxial Assembly Constraints Imposed on Amyloid ß25-35 Fibrils

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Amyloid fibrils are filamentous aggregates deposited in extracellular tissue in various neurodegenerative and protein misfolding disorders. Amyloid ß (Aß) peptides form self-associating fibrillar structures in Alzheimer's disease. The Aß25-35 peptide is thought to represent the biologically active, toxic fragment of the full-length beta peptide.

We have previously shown that Aß25-35 forms an oriented network on mica by epitaxial assembly mechanisms that significantly accelerate fibril growth. Whether the structure of the epitaxially grown fibrils is identical to that of the fibrils assembled under equilibrium conditions is not known. To explore these differences, we investigated fibril structure and dynamics with AFM, force spectroscopic, and fluorescence and absorption spectroscopic methods. To facilitate fluorescence labeling, we employed a mutant peptide, Aß25-35_N27C, which was labeled with TMRIA. The nanomechanical behavior of Aß25-35 fibrils was characterized by the appearance of force staircases which correspond to the force-driven unzipping and dissociation of protofilaments. The elementary plateau force was 30 pN for both the epitaxially-grown fibrils and for the fibrils assembled in solution. The average fibril height was 1-3 nm for the epitaxially-grown fibrils, whereas fibrils grown in solution were 3-15 nm thick. Unlike epitaxialy-grown fibrils, the fibrils assembled in solution displayed a helical structure with 30-50 nm periodicity. Whereas fibril assembly in solution occurred on a time scale of hours to days, on mica surface fibrils appeared within a few minutes. In the absorption spectra of TMRIA-labeled Aß25-35_N27C, a significant peak at 518 nm corresponding to rhodamine dimmers appeared rapidly, suggesting that peptide dimerization is a fast process, and the rate limiting step of fibril growth lies further along the assembly pathway.

1106-Pos Board B16

The Nature of the Amyloid-β Monomer and the Monomer-Oligomer Equilibrium

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Abstract:

The monomer to oligomer transition initiates the aggregation and pathogenic transformation of Alzheimer's Amyloid-β (Aβ) peptide. However, the monomeric state of this aggregation-prone peptide has remained beyond the reach of most experimental techniques, and a quantitative understanding of this transition is yet to emerge. Here we employ single molecule level fluorescence tools to characterize the monomeric state and the monomer-oligomer transition at appropriately low concentrations in buffers mimicking the cerebrospinal fluid (CSF). Our measurements show the monomer to be a compact object with a hydrodynamic radius of 0.9 ± 0.1 nm, which confirms the prediction made by some of the *in silico* studies. Surprisingly, at equilibrium, both $A\beta_{40}$ and $A\beta_{42}$ remain predominantly monomeric up to 1.5 μM concentration. This concentration is much higher than their estimated concentrations in the CSF of either normal or diseased brains. However, we find that a strong kinetic barrier impedes the dissociation of pre-formed oligomers. Since Aβ oligomers in the CSF are generally accepted to be the key agents in Alzheimer's pathology, our results imply that these are released in the CSF as pre-formed entities, and their metastability allows them to remain toxic. We conclude that thermodynamic principles allow the development of pharmacological agents that can catalytically convert these metastable species to non-toxic monomers.